

PATENT SPECIFICATION

(11) 1338547

NO DRAWINGS

- (21) Application No. 15774/72 (22) Filed 5 April 1972
 (31) Convention Application No. 135757 (32) Filed 20 April 1971
 (31) Convention Application No. 223339 (32) Filed 3 Feb. 1972 in
 (33) United States of America (US)
 (44) Complete Specification published 28 Nov. 1973
 (51) International Classification C07C 173/00//169/24 169/12
 (52) Index at acceptance
 C2U 4A1 4A2 4C4 4C5 4X 6

(54) NOVEL 17 β -(TETRAHYDROPYRAN-4-YLOXY) STEROIDS

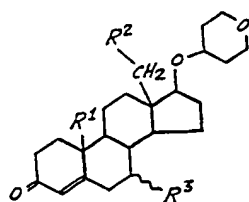
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SPECIFICATION No. 1,338,547

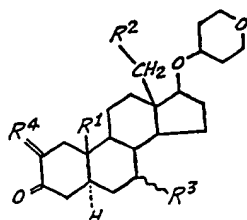
- Page 2, line 104, for analobic read anabolic
 Page 3, line 96, for of read or
 Page 4, line 19, delete of insert —
 Page 4, line 33, delete a
 Page 4, line 62, for 2-en read 4-en
 Page 5, line 36, for 2-1/2 read 2 1/2
 Page 5, line 48, for triturated read titrated
 Page 5, line 96, for 5-one read 3-one
 Page 6, line 27, for 400 ml read 40 ml
 Page 6, line 114, for 1,3,5(10- read 1,3,5(10)-
 Page 6, line 120, for (1.5g. read (1.5g.)
 Page 7, line 110, after hexane insert to yield
 Page 7, line 112, after 5 α - insert androstan-

THE PATENT OFFICE
 22nd January, 1974

20 The novel compounds of the present invention bearing said novel group can be further represented by the following structural formulas:



(A)



(B)

[Price 25p]

R⁵

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in which R⁵ is hydrogen or methyl; and
 R⁶ is hydrogen, hydrocarbon carboxylic
 acyl of less than twelve carbon atoms, or
 alkyl of one to eight carbon atoms.

Thus included within the scope of the
 novel compounds of the present invention are
 the following:

- 17 β - (tetrahydropyran - 4 - yloxy) - estr-
 4 - en - 3 - one;
 17 β - (tetrahydropyran - 4 - yloxy)-
 androst - 4 - en - 3 - one; 40
 7 α - methyl - 17 β - (tetrahydropyran-
 4 - yloxy) - estr - 4 - en - 3 - one;
 7 β - methyl - 17 β - (tetrahydropyran-
 4 - yloxy) - estr - 4 - en - 3 - 45
 one;
 7 α - methyl - 17 β - (tetrahydropyran-
 4 - yloxy) - androst - 4 - en - 3 -
 one;
 7 β - methyl - 17 β - (tetrahydropyran-
 4 - yloxy) - androst - 4 - en - 3 - 50
 one;
 and the corresponding 18 - methyl and 18-
 ethyl compounds thereof;

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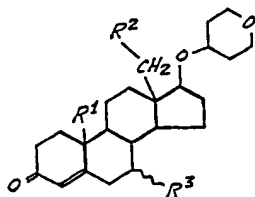
(54) NOVEL 17β-(TETRAHYDROPYRAN-4-YLOXY) STEROIDS

(71) We, SYNTEX CORPORATION, a Panamanian Corporation of Apartado Postal 7386, Panama, Panama, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

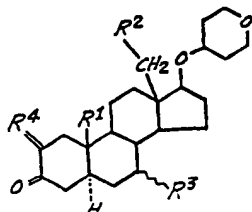
The present invention relates to novel steroid ethers. More particularly, the present invention is related to steroid ethers of the androstane and estrane series in which the novel tetrahydropyran - 4 - yloxy ether grouping is attached at the C-17β position and can be depicted by the following formula:



The novel compounds of the present invention bearing said novel group can be further represented by the following structural formulas:

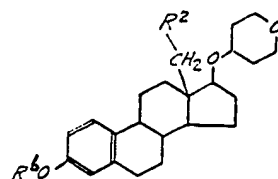


(A)



(B)

[Price 25p]



(C)

In the above and succeeding formulas:

- R¹ is hydrogen or methyl; 25
 R² is hydrogen, methyl, or ethyl;
 R³ is hydrogen, α - methyl, or β - methyl;
 R⁴ is hydroxymethylene or the group



in which R¹ is hydrogen or methyl; and

R⁶ is hydrogen, hydrocarbon carboxylic acyl of less than twelve carbon atoms, or alkyl of one to eight carbon atoms.

Thus included within the scope of the novel compounds of the present invention are the following:

- 17β - (tetrahydropyran - 4 - yloxy) - estr-4 - en - 3 - one;
 17β - (tetrahydropyran - 4 - yloxy)- androst - 4 - en - 3 - one; 40
 7α - methyl - 17β - (tetrahydropyran-4 - yloxy) - estr - 4 - en - 3 - one;
 7β - methyl - 17β - (tetrahydropyran-4 - yloxy) - estr - 4 - en - 3 - one; 45
 7α - methyl - 17β - (tetrahydropyran-4 - yloxy) - androst - 4 - en - 3 - one;
 7β - methyl - 17β - (tetrahydropyran-4 - yloxy) - androst - 4 - en - 3 - one; 50

and the corresponding 18 - methyl and 18-ethyl compounds thereof;

- 17 β - (tetrahydropyran - 4 - yloxy)-
5 α - estran - 3 - one;
17 β - (tetrahydropyran - 4 - yloxy)-
5 α - androstan - 3 - one;
5 7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - estran - 3 - one;
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - estran - 3 - one;
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 - one;
10 7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 -
one;

and the corresponding 18 - methyl and 18-
ethyl compounds thereof;

- 2 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - estran - 3 - one;
2 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 - one;
20 2 - hydroxymethylene - 17 β - (tetrahydro-
pyran - 4 - yloxy) - 5 α - estran - 3 -
one;
2 - hydroxymethylene - 17 β - (tetrahydro-
pyran - 4 - yloxy) - 5 α - androstan - 3 -
one;

and the corresponding 7 α - methyl, 7 β -
methyl, 18 - methyl, 18 - ethyl, 7 α ,18 -
dimethyl, 7 α - methyl - 18 - ethyl, 7 β ,18 -
dimethyl, and 7 β - methyl - 18 - ethyl
30 compounds thereof;

- 17 β - (tetrahydropyran - 4 - yloxy)-
estra - 1,3,5(10) - trien - 3 - ol;
3 - methoxy - 17 β - (tetrahydropyran-
4 - yloxy) - estra - 1,3,5(10) - triene;
35 3 - acetoxy - 17 β - (tetrahydropyran-
4 - yloxy) - estra - 1,3,5(10) - triene;
3 - benzyloxy - 17 β - (tetrahydropyran-
4 - yloxy) - estra - 1,3,5(10) - triene;
and the 18 - methyl and 18 - ethyl com-
pounds thereof.

Particularly valuable compounds hereof are
17 β - (tetrahydropyran - 4 - yloxy) - androst-
4 - en - 3 - one, 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 - one, and
45 17 β - (tetrahydropyran - 4 - yloxy) - estra-
1,3,5(10) - trien - 3 - ol.

The compounds of the present invention
of formulas (A) and (B) exhibit high anabolic
and androgenic activity and are thus useful
50 for those purposes for which such activity
is indicated, for example, in treatment to
enhance weight gain and in the treatment
of debilitated patients, particularly those
recovering in post-operative care. They can
55 also be used in the treatment of male climac-
teric and dismenorrhea in the female. The
compounds of the present invention of
Formula (C) exhibit high oral estrogenic and
antifertility activity and are useful for the
60 purposes for which such activity is indicated
for example, in the treatment of perimenopau-
sal conditions and the control and regula-
tion of fertility. These compounds can be
employed in the same manner as steroid
65 compounds having similar activity, such as

oxymetholone, norethandrolone, dromostano-
lone, testosterone propionate, mestranol,
estradiol and conjugated estrogens, and pro-
vide the benefits and advantages of oral
administration because of their high oral activi-
ties. The present invention includes pharma-
ceutical compositions comprising compounds
of Formulae A, B and C in suitable excipi-
ents.

The prior art has reported certain related
steroid ethers including 17 β - (tetrahydro-
pyran - 2 - yloxy) - androst - 4 - en - 3 -
one, 17 β - (tetrahydropyran - 2 - yloxy)-
5 α - androstan - 3 - one, and 17 β - (tetra-
hydropyran - 2 - yloxy) - estra - 1,3,5(10)-
trien - 3 - ol.

Now it has been discovered that the com-
pounds of the present invention possess unex-
pected and unobvious anabolic and androgenic
and estrogenic and anti-fertility activity which
is superior to that exhibited by compounds of
the closest prior art. Thus, standard tests were
conducted for anabolic/androgenic activity
which are modifications of the basic methods
described by Hershberger et al., Proc. Soc.
Expt. Biol. Med. 83, 175 (1953) and by
Dorfman, Methods in Hormone Research,
Academy Press, N.Y. (1962), p. 306 of Vol.
II. These tests demonstrated that 17 β -
(tetrahydropyran - 4 - yloxy) - androst-
4 - en - 3 - one has equal to or greater
than three times the androgenic activity of
17 β - (tetrahydropyran - 2 - yloxy) - androst-
4 - en - 3 - one. This is of particular import-
ance when treatment requiring high androgenic
activity is indicated. Similarly, these tests
demonstrated that 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 - one has
greater than four times the anabolic activity
and two times the androgenic activity of 17 β -
(tetrahydropyran - 2 - yloxy) - 5 α - andro-
stan - 3 - one. This is significant when treat-
ment requiring either or both anabolic and
androgenic activity is/are indicated.

Standard tests were conducted for estro-
genic and anti-fertility activity. These tests
demonstrated that 17 β - (tetrahydropyran-
4 - yloxy) - estra - 1,3,5(10) - trien - 3 -
ol has about two times the oral estrogenic
activity of, at least four times the prolonged
oral estrogenic activity of, and up to four
times the oral anti-fertility activity of 17 β -
(tetrahydropyran - 2 - yloxy) - estra - 1,3,
5(10) - trien - 3 - ol. This is significant when
treatment requiring high or prolonged estro-
genic and anti-fertility activity is indicated.

The compounds of the present invention
have thus been shown to be unexpectedly bio-
logically superior to the compounds of the
prior art because they possess androgenic
and/or anabolic or estrogenic and/or anti-
fertility activity far in excess of that which
could be predicted.

In addition, it has been surprisingly dis-
covered that the compounds of the present

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invention, in contrast to the ethers of the prior art, are stable to hydrolysis conditions such as those which are encountered in the animal stomach. The suitability for oral

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administrations of the compounds is thus enhanced.
The compounds of the present invention are prepared directly by treating the corresponding

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17 β - hydroxy starting compound with a 4 - halotetrahydropyran in organic liquid reaction media, such as benzene, glyme, and dimethylformamide at a temperature of from about 50°C to about the reflux temperature of the solvent and with the use of a suitable

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base, such as sodium or lithium hydride or silver oxide.

Alternatively, 3 - keto - Δ^4 - 17 β - ol starting compounds are treated with 4 - methoxy - 5,6 - dihydro - 2H - pyran in the presence of acid to give the corresponding

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17 β - (4 - methoxy - tetrahydropyran - 4 - yloxy) compounds. These are then treated with an acid anhydride or acid chloride in the presence of sodium methoxide in dimethyl sulfoxide. The resultant 3 - acyloxy - $\Delta^{3,5}$ compounds are then reduced such as with sodium borohydride to give the corresponding

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3 β - hydroxy - Δ^3 compounds. These compounds are then treated with lithium aluminium hydride/aluminium chloride to give the corresponding

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3 β - hydroxy - 17 β - (tetrahydropyran - 4 - yloxy) - Δ^3 compounds. These compounds are then converted to the corresponding 3 - keto - Δ^4 compounds hereof under Oppenauer conditions, and the 3 - keto - Δ^4 compounds are converted, if desired, to the corresponding 5 α compounds hereof under Birch conditions. The Δ^3 - 3 β - ols are converted to the corresponding 5 α compounds by palladium-on-charcoal hydrogenation, followed by oxidation, for example with chromic acid, to give the corresponding 3 - keto - 5 α compounds. The corresponding 2 - hydroxy - methylene - 3 - keto - 5 α compounds (prepared by treating the 3 - keto - 5 α compounds with ethyl formate in a base) are hydrogenated to prepare the corresponding

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2 α - methyl - 3 - keto - 5 α compounds.

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An alternative procedure for producing the 3 β - hydroxy - 17 β - (tetrahydropyran - 4 - yloxy) - Δ^3 compounds comprises firstly treating 3 β - acyloxy - Δ^3 - 17 β - ol starting compounds with 4 - methoxy - 5,6 - dihydro - 2H - pyran in the presence of acid to give the corresponding

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17 β - (4 - methoxytetrahydropyran - 4 - yloxy) compounds, followed by treatment with lithium aluminium hydride/aluminium chloride to give the corresponding

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3 β - hydroxy - 17 β - (tetrahydropyran - 4 - yloxy) - Δ^3 compounds. A similar procedure can be employed to produce the 17 β - (tetrahydropyran - 4 - yloxy) - estrane - 1,3,5(10)-trien - 3 β - ols of the present invention from the corresponding 3 β - acyloxyestrane - 1,3,5

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(10) - trien - 17 β - ols.

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An alternative procedure for obtaining the 3 β - hydroxy - 5 α intermediate compounds starts with the corresponding 3 β - acyloxy - Δ^3 - 17 - one compounds. These are hydrogenated, for example with palladium-on-charcoal to give the corresponding 5 α compounds which are then reduced, for example with sodium borohydride, to give the corresponding 17 β - ols. These are then treated with 4 - methoxy - 5,6 - dihydro - 2H - pyran in the presence of acid to give the corresponding 17 β - (4 - methoxy - tetrahydropyran - 4 - yloxy) compounds, which are in turn hydrolysed to the corresponding 3 β - ols and then treated with aluminium chloride/lithium aluminium hydride to give the corresponding 3 β - hydroxy - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α compounds.

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In the Ring A aromatic series, the lithium aluminium hydride/aluminium chloride or 4-halotetrahydropyran reactions are preferably conducted on the 3 - alkoxy ether starting compounds or the 3 - hydroxy starting compounds followed by conventional esterification of the latter, if desired. If the reactions are conducted on a 3 - acyloxy starting compound, this group will be cleaved in the course of the reactions.

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The starting compounds of the present invention can be selected from the estrane (R¹=H) of androstane (R¹=methyl) series. The starting compounds can further be of the normal (R²=H) or C-18 substituted (R²=methyl or ethyl) series. Similarly, the starting compounds of the present invention can bear a 7 α - methyl or 7 β - methyl group (R³). If desired, 2 α - methyl - 3 - keto - 5 α - estrane and androstane compounds can be employed as starting materials with introduction of the C-17 β novel ether grouping herein conducted as described above.

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By the term "alkyl" is meant a monovalent aliphatic saturated hydrocarbon group of one to eight carbon atoms, i.e., methyl, ethyl, n - propyl, isopropyl, n - butyl, isobutyl, sec-butyl, t - butyl, n - pentyl, isopentyl, hexyl, heptyl, octyl, and the various isomers thereof. By the term "hydrocarbon carboxylic acyl" is meant an acyl group of less than 12 carbon atoms and derived from a substituted or unsubstituted (hydrocarbon) carboxylic acid. These acids can be completely saturated or possess varying degrees of unsaturation (including aromatic), can be of straight chain, branched chain, or cyclic structure. In addition, they can be substituted by functional groups, for example, hydroxy, alkoxy containing up to six carbon atoms, acyloxy, nitro, amino, and halogeno, attached to the hydrocarbon backbone chain. Typical acyl groups include acetyl, propionyl, butyryl, trimethylacetyl, valeryl, methyl ethylacetyl, caproyl, t - butylacetyl, decanoyl, undecanoyl, benzoyl, phenylacetyl, diphenylacetyl, cyclopentylpropionyl, methoxyacetyl, aminoacetyl, diethylaminoacetyl, tri-

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chloroacetyl, β - chloropropionyl and adamantoyl.

The following examples further illustrate the method by which the present invention can be practiced.

Example 1

Ten g. of 3β - acetoxyandrost - 5 - en - 17β - ol in 150 ml. of ether and 150 mg. of *p* - toluenesulfonic acid (dried by azeotropic distillation from benzene) are mixed together and the reaction mixture is treated with 4 - methoxy - 5,6 - dihydro - 2H - pyran, 1 ml. at a time until reaction is complete (followed by tlc). The reaction is quenched by addition of 0.5 ml. of triethylamine, and the reaction mixture is washed with water. Careful crystallization from methanol containing pyridine then gives 3β - acetoxy of 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 5 - ene.

A solution of 14 g. of aluminium chloride in 250 ml. dry ether is treated with a solution of 4 g. of lithium aluminium hydride in 100 ml. of ether. 3β - Acetoxy - 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 5 - ene (1.5 g.) is added to the solution. An additional 7 g. of the steroid is added to the lithium aluminium hydride solution. After reduction is complete (monitored by tlc), saturated aqueous sodium chloride solution is added until a precipitate forms. This is filtered and the crude product purified by a chromatography on silica gel to yield 17β - (tetrahydropyran - 4 - yloxy) - androst - 5 - en - 3β - ol.

Two hundred mg. of 17β - (tetrahydropyran - 4 - yloxy) - androst - 5 - en - 3β - ol in 25 ml. of toluene containing 1 ml. of cyclohexanone is distilled briefly to remove moisture. Freshly distilled aluminium isopropoxide (200 mg.) is added and the mixture is refluxed for 18 hours. The product is isolated by steam distillation, extraction and chromatography to yield 17β - (tetrahydropyran - 4 - yloxy) - androst - 4 - en - 3 - one.

Example 2

Ten g. of androst - 4 - en - 17β - ol - 3 - one in 150 ml. of ether and 150 mg. of *p* - toluene sulfonic acid (dried by azeotropic distillation from benzene) are mixed together and the reaction mixture is treated with 4 - methoxy - 5,6 - dihydro - 2H - pyran, 1 ml. at a time until reaction is complete (followed by tlc). The reaction is quenched by addition of 0.5 ml. of triethylamine and the reaction mixture is washed with water. Careful crystallization from methanol containing pyridine then gives 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 4 - en - 3 - one.

The 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 2 - en - 3 - one (2 g.) is dissolved in 20 ml. of dry dimethyl sul-

fide and the solution is heated with one molar equivalent of sodium methoxide under nitrogen at 5 to 10°C. After 20 minutes, there is added one molar equivalent of acetic anhydride or acetyl chloride. After one hour saturated brine is added and the precipitate of 3 - acetoxy - 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 3,5 - diene is collected, washed with water and carefully dried.

Alternatively, 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 4 - en - 3 - one (2 g.) is dissolved in tetrahydrofuran (25 ml.) containing 1.2 equivalents of pure potassium *t* - butoxide. After 20 minutes there is added one molar equivalent of acetic anhydride or acetyl chloride (neat or dissolved in 10 ml. of tetrahydropyran). After one hour, saturated brine (250 ml.) is added and the 3 - acetoxy - 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 3,5 - diene is isolated by extraction with ethyl acetate.

Twenty g. of 3 - acetoxy - 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 3,5 - diene in 150 ml. of dioxane is reduced by the addition of sodium borohydride in aqueous dioxane until the reaction is complete. The mixture is poured onto a little dilute hydrogen chloride and ice, filtered, washed to neutral, dried, and recrystallized from methanol to yield 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - androst - 5 - en - 3β - ol.

A solution of 14 g. of aluminium chloride in 250 ml. of dry ether is treated with a solution of 4 g. of lithium aluminium hydride in 100 ml. of ether. 17β - (4 - Methoxytetrahydropyran - 4 - yloxy) - androst - 5 - en - 3β - ol (1.5 g.) is added to the solution. An additional 7 g. of the steroid is added to the lithium aluminium hydride solution. After reduction is complete (monitored by tlc), saturated aqueous sodium chloride solution is added until a precipitate forms. This is filtered and the crude product purified by chromatography on silica gel to yield 17β - (tetrahydropyran - 4 - yloxy) - androst - 5 - en - 3β - ol.

Two hundred mg. of 17β - (tetrahydropyran - 4 - yloxy) - androst - 5 - en - 3β - ol in 25 ml. of toluene containing 1 ml. of cyclohexanone is distilled briefly to remove moisture. Freshly distilled aluminium isopropoxide (200 mg.) is added and the mixture is refluxed for 18 hours. The product is isolated by steam distillation, extraction and chromatography to yield 17β - (tetrahydropyran - 4 - yloxy) - androst - 4 - en - 3 - one.

The other 3 - keto compounds of the present invention bearing a novel 17β - (tetrahydropyran - 4 - yloxy) ether grouping can be prepared from the corresponding starting materials. Thus, for example, there are prepared:

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- 17 β - (tetrahydropyran - 4 - yloxy) - estr-
4 - en - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - estr - 4 - en - 3 -
5 one,
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) estr - 4 - en - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - androst - 4 - en - 3 -
10 one,
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - androst - 4 - en - 3 -
one,
15 17 β - (tetrahydropyran - 4 - yloxy) - 18 -
methylestr - 4 - en - 3 - one,
17 β - (tetrahydropyran - 4 - yloxy) - 18 -
methylandrost - 4 - en - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - androst - 4 -
20 en - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - ester - 4 -
en - 3 - one,
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - ester - 4 -
25 en - 3 - one, and
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - androst - 4 -
en - 3 - one.
- 17 β - (tetrahydropyran - 4 - yloxy)-
5 α - estran - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - estran - 3 - one, 65
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - estran - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 - 70
one,
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 5 α - androstan - 3 -
one,
17 β - (tetrahydropyran - 4 - yloxy)- 75
18 - methyl - 5 α - estran - 3 -
one,
17 β - (tetrahydropyran - 4 - yloxy)-
18 - methyl - 5 α - androstan - 3 - 80
one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - 5 α - andro-
stan - 3 - one,
7 α - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - 5 α - estran- 85
3 - one,
7 β - methyl - 17 β - (tetrahydropyran-
4 - yloxy) - 18 - methyl - 5 α - estran-
3 - one, and
7 β - methyl - 17 β - (tetrahydropyran- 90
4 - yloxy) - 18 - methyl - 5 α - andro-
stan - 3 - one.

30 Example 3

To a solution of 1 g. of 17 β - (tetra-
hydropyran - 4 - yloxy) - androst - 4 - en-
3 - one in 75 ml. of tetrahydrofuran and 125
35 ml. of liquid ammonia is added over a 20-
minute period 0.27 g. of lithium. The mix-
ture is refluxed with stirring for 2-1/2 hours
and its color then discharged by the care-
ful addition of ethanol. The resulting solu-
tion is allowed to stand at room temperature
40 until the ammonia has evaporated and the
residue is next shaken with 100 ml. of 1:1
water:methylene chloride. The aqueous layer
is separated and extracted with methylene
45 chloride and the combined extracts and organic
layer are dried over magnesium sulfate and
evaporated. This residue is dissolved in 100
ml. of 5:9 methylene chloride:acetone and
trituated with 8N chromic acid, maintaining
50 a temperature of 25°C. Thirteen milliliters
of water are then added with gentle shaking
and the aqueous phase is separated and extrac-
ted with methylene chloride. The combined
extracts and organic layer are dried over mag-
55 nesium sulfate and evaporated to dryness to
yield 17 β - (tetrahydropyran - 4 - yloxy)-
5 α - androstan - 3 - one which may be
further purified through recrystallization from
ether:hexane.

In a similar manner, the compounds pre-
pared as described in Examples 1 and 2 above
60 are thus treated to prepare the corresponding
3 - keto - 5 α - compounds:

Example 4

To a stirred solution of 3 g. of 17 β - (tetra-
hydropyran - 4 - yloxy) - 5 α - androstan-
5 - one in 60 ml. of anhydrous benzene is
added, with cooling and under nitrogen, a sus-
pension of 3 ml. of ethyl formate and 1.3 g.
of sodium hydride in mineral oil. The mixture
is stirred at room temperature for 24 hours
100 and hexane is then added until complete
precipitation occurs. The solid which forms
is collected, dried under vacuum and sus-
pended in aqueous hydrochloric acid. This
suspension is stirred at room temperature for
105 half an hour and then filtered. The solid
thus collected is washed with water and dried
to yield 2 - hydroxymethylene - 17 β - (tetra-
hydropyran - 4 - yloxy) - 5 α - androstan-
3 - one which is recrystallized from methylene
110 chloride:hexane.

In a similar manner, the corresponding 2-
hydroxy - methylene compounds of the other
compounds prepared as set forth in Example
3 can be prepared, for example, 115

- 2 - hydroxymethylene - 17 β - (tetrahydro-
pyran - 4 - yloxy) - 5 α - estran - 3 -
one,
2 - hydroxymethylene - 7 α - methyl - 17 β -
(tetrahydropyran - 4 - yloxy) - 5 α - 120
estran - 3 - one,
2 - hydroxymethylene - 7 β - methyl - 17 β -
(tetrahydropyran - 4 - yloxy) - 5 α -
estran - 3 - one,
2 - hydroxymethylene - 7 α - methyl - 17 β - 125

- (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one,
 2 - hydroxymethylene - 7 β - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one,
 2 - hydroxymethylene - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - estran - 3 - one,
 2 - hydroxymethylene - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - androstan - 3 - one,
 2 - hydroxymethylene - 7 α - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - androstan - 3 - one,
 2 - hydroxymethylene - 7 α - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - estran - 3 - one,
 2 - hydroxymethylene - 7 β - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - estran - 3 - one, and
 2 - hydroxymethylene - 7 β - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - androstan - 3 - one.

Example 5

- A mixture of 5 g. of 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one in 400 ml. of anhydrous thiophene-free benzene, 2 ml. of ethyl formate and 1.5 g. of sodium hydride is stirred for eight hours under nitrogen. The solid which forms is collected by filtration, washed with benzene and then hexane and dried in vacuo. This material is then cautiously added in portions to excess ice-cold dilute hydrochloric acid with stirring. The solid which forms is collected by filtration, washed with water and air dried. One gram of the product in 15 ml. of methanol is hydrogenated with 0.4 g. of prehydrogenated 10% palladium carbon catalyst at 25°C atmospheric pressure until two moles of hydrogen are absorbed. The mixture is then filtered, the catalyst is washed with hot methanol and the combined solutions are evaporated to dryness to yield 2 α - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one.

- In a similar manner, the compounds prepared as described in Example 3 above can be converted to the corresponding 2 α - methyl compounds, for example,

- 2 α - methyl - 17 β - tetrahydropyran - 4 - yloxy) - 5 α - estran - 3 - one,
 2 α ,7 α - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - estran - 3 - one,
 2 α ,7 β - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - estran - 3 - one,
 2 α ,7 α - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one,
 2 α ,7 β - dimethyl - 17 β - (tetrahydro-

- pyran - 4 - yloxy) - 5 α - androstan - 3 - one,
 2 α - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - estran - 3 - one,
 2 α - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - androstan - 3 - one,
 2 α ,7 α - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - androstan - 3 - one,
 2 α ,7 α - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - estran - 3 - one,
 2 α ,7 β - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - estran - 3 - one, and
 2 α ,7 β - dimethyl - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5 α - androstan - 3 - one.

Example 6

- A solution of 3 g. of 2 - hydroxymethylene - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one in 125 ml. of dioxane is hydrogenated at 25°C/570 mm. with 0.5 g. of pre-hydrogenated 10% palladium-on-charcoal. Upon the consumption of the theoretical amount of hydrogen, the solution is filtered and the filtrate evaporated to dryness under reduced pressure to yield 2 α - methyl - 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one which is recrystallized from acetone.

In a similar manner, the products of the procedure of Example 4 above can be converted to the corresponding 2 α - methyl compounds.

Example 7

- Ten g. of 3 - acetoxystera - 1,3,5(10) - trien - 17 β - ol in 150 ml. of ether and 150 mg. of *p* - toluenesulfonic acid (dried by azeotropic distillation from benzene) are mixed together and the reaction mixture is treated with 4 - methoxy - 5,6 - dihydro-2H - pyran, 1 ml. at a time until reaction is complete (followed by tlc). The reaction is quenched by addition of 0.5 ml. of triethylamine, and the reaction mixture is washed with water. Careful crystallization from methanol containing pyridine then gives 3 - acetoxy - 17 β - (4 - methoxytetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - triene.

A solution of 14 g. of aluminium chloride in 250 ml. dry ether is treated with a solution of 4 g. of lithium aluminium hydride in 100 ml. of ether. 3 - Acetoxy - 17 β - (4 - methoxy - tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - triene (1.5 g. is added to the solution. An additional 7 g. of steroid is added to the lithium aluminium hydride solution. After reduction is complete (monitored by tlc), saturated sodium chloride is added until a precipitate forms. This is filtered and the crude product purified by

chromatography on silica gel to yield 17 β -(tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - trien - 3 - ol.

- 5 Alternatively, a solution of 100 mg. of lithium aluminium hydride in ether is added to a solution of 1.2 g. of aluminium chloride in ether and cooled in ice. The resultant solution is stirred at room temperature for one hour and then 200 mg. of 3 - acetoxy-
10 17 β - (4 - methoxytetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - triene are added. The solution is refluxed for two hours (followed by tlc). The solution is then chromatographed with ether:hexane to give 17 β -
15 (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - trien - 3 - ol which can be recrystallized from methanol.

- In like manner 17 β - (tetrahydropyran-4 - yloxy) - 18 - methyl - estra - 1,3,5(10)-
20 trien - 3 - ol, 3 - methoxy - 17 β - (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10)-triene, 3 - methoxy - 17 β - tetrahydropyran-4 - yloxy) - 18 - methyl - estra - 1,3,5(10)-triene, 3 - ethoxy - 17 β - (tetrahydropyran-4 - yloxy) - estra - 1,3,5(10) - triene, and
25 3 - ethoxy - 17 β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - estra - 1,3,5(10) - triene is each prepared from the respective starting compound, the 3 - ol compound first
30 mentioned being obtained as described above starting with the e.g. 3 - acetate compound.

Example 8

- A mixture of 2 g. of 17 β - (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - trien-
35 3 - ol in 8 ml. of pyridine and 4 ml. of benzoyl chloride is heated at steam bath temperature for one hour. The mixture is then poured into ice water and the solid which forms is collected by filtration, washed with
40 water and dried to yield 3 - benzoyloxy-17 β - (tetrahydropyran - 4 - yloxy) - estra-1,3,5(10) - triene which is further purified through recrystallization from methylene chloride:hexane.

- 45 In like manner, 3 - acetoxy - 17 β - (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - triene is prepared using acetyl chloride. The other hydrocarbon carboxylic acyl compounds are also thus prepared, using the
50 appropriate acyl chloride. Similarly, 3 - acetoxy - 17 β - (tetrahydropyran - 4 - yloxy)-18 - methyl - estra - 1,3,5(10) - triene and 3 - benzoyloxy - 17 β - (tetrahydropyran-4 - yloxy) - 18 - methylestra - 1,3,5(10) -
55 triene are prepared.

Example 9

- A suspension of 0.5 g. of 5% palladium-on carbon catalyst in 50 ml. of methanol is hydrogenated for 30 minutes. A solution of
60 2 g. of 17 β - (tetrahydropyran - 4 - yloxy)-androst - 5 - en - 3 β - ol in 200 ml. of methanol is added and hydrogenated with

agitation until the uptake of hydrogen has ceased. The catalyst is removed by filtration and the solution evaporated to yield 17 β -
65 (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 β - ol which is recrystallized from methylene chloride:hexane for further purification.

To a stirred solution of 1 g. of 17 β -
70 (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 β - ol in 10 ml. of acetone, cooled to 0°C, is added under nitrogen a solution of 8N chromic acid (prepared by mixing 26 g. of chromium trioxide with 23 ml. of concentrated
75 sulfuric acid and diluting with water to 100 ml.) until the color of the reagent persists in the mixture. The mixture is then stirred for 5 minutes at 0—5°C and diluted with water. The solid which forms is collected
80 by filtration, washed with water and dried under vacuum to yield 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one which may be further purified by recrystallization from acetone:hexane.
85

Example 10

A mixture of 1 g. of 5 α - androstan-17 β - ol - 3 - one and 5 g. of 4 - iodo-
tetrahydropyran in 25 ml. of benzene is distilled under nitrogen to remove moisture.
90 Three g. of silver carbonate are then added and the mixture refluxed for 3 hours. The mixture is then chromatographed (7:1 hexane:ethyl acetate) over silica gel to give
95 17 β - (tetrahydropyran - 4 - yloxy) - 5 α - androstan - 3 - one.

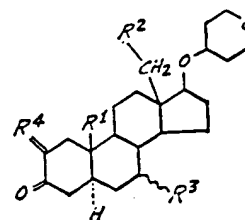
Example 11

Forty g. of 3 β - acetoxyandrost - 5 - en - 17 - one in 1.4 l. of ethanol is hydrogenated with 5 g. of 10% palladium-on-char-
100 coal to yield 3 β - acetoxy - 5 α - androstan-17 - one.

3 β - Acetoxy - 5 α - androstan - 17 - one (25 g.) in 300 ml. of dioxane and 10% water is cooled to 0°C. Sodium borohydride
105 (ca. 3 g.) is added. After the reduction is complete, the mixture is poured into water, ice and dilute hydrogen chloride. The resultant mixture is filtered and crystallized from benzene: hexane 3 β - acetoxy - 5 α - androstan-17 β - ol.
110

3 β - Acetoxy - 5 α - 17 β - ol (14 g.) is dispersed in 150 ml. of ether. P - toluenesulfonic acid (100 mg.) in benzene (dried azeotropically) is added to the solution. 4 -
115 Methoxy - 5,6 - dihydro - 2H - pyran is added 1 ml. at a time over 6 hours. The mixture is quenched with triethylamine, and the reaction mixture is washed with water. Careful crystallization from methanol containing
120 pyridine then gives 3 β - acetoxy - 17 β - (4 - methoxytetrahydropyran - 4 - yloxy) 5 α - androstane.

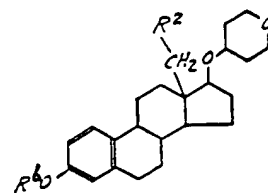
- Hydrolysis with potassium hydroxide in methanol gives 17β - (4 - methoxytetrahydropyran - 4 - yloxy) - 5α - androstan - 3β - ol. This compound is treated with aluminium chloride: lithium aluminium hydride, as described above, to give 17β - (tetrahydropyran - 4 - yloxy) - 5α - androstan - 3β - ol which is oxidized (Jones), as described above, to give 17β - (tetrahydropyran - 4 - yloxy) - 5α - androstan - 3 - one.



(B)

50

- Example 12**
A mixture of 2 grams of estra - 1,3,5(10) - trien - 3 - ol - 17 - one in 8 ml. of pyridine and 4 ml. of acetyl chloride is heated at steam bath temperatures for one hour. The mixture is then poured into ice water and the solid which forms is collected by filtration, washed with water and dried to yield 3 - acetoxyestra - 1,3,5(10) - trien - 17 - one which is further purified through recrystallization from methylene chloride: hexane.



(C)

- A solution of 2 g. of 3 - acetoxyestra - 1,3,5(10) - trien - 17 - one in 20 ml. of anhydrous tetrahydrofuran is cooled to -75°C in a dry ice-acetone bath and treated with a previously cooled solution of 0.6 g. of lithium tri - t - butoxy aluminium hydride in 20 ml. of anhydrous tetrahydrofuran. After maintaining the reaction mixture at reflux for 15 minutes it is cooled and poured into ice water and extracted several times with ethyl acetate. These extracts are washed with water to neutrality, dried over anhydrous sodium sulfate and evaporated to dryness to yield 3 - acetoxyestra - 1,3,5(10) - trien - 17β - ol.

wherein

- R^1 is hydrogen or methyl;
 R^2 is hydrogen, methyl or ethyl;
 R^3 is hydrogen, α - methyl, or β - methyl;
 R^4 is hydroxymethylene or the group

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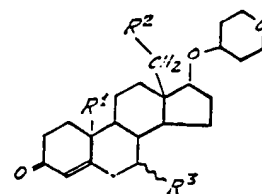


in which R^5 is hydrogen or methyl; and R^6 is hydrogen, hydrocarbon carboxylic acyl of less than twelve carbon atoms, or alkyl, of one to eight carbon atoms.

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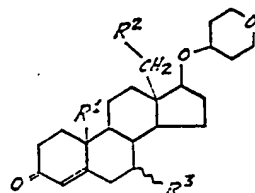
2. A compound selected from those of Claim 1 of the formula:

- Similarly prepared are 3 - acetoxy - 18 - methylestra - 1,3,5(10) - trien - 17β - ol and 3 - acetoxy - 18 - ethylestra - 1,3,5(10) - trien - 17β - ol. The thus-prepared compounds can then be used, as described in Example 7, to prepare compounds of the present invention.



45 WHAT WE CLAIM IS:—

1. A compound selected from the group of compounds represented by the following formulas:



(A)

wherein each of R^1 , R^2 , and R^3 is as therein defined.

65

3. A compound selected from those of Claim 2 wherein R^3 is α - methyl.

4. A compound selected from those of Claim 2 wherein R^3 is hydrogen.

70

5. The compound selected from those of Claim 4 wherein each of R^1 and R^2 is hydrogen; 17β - (tetrahydropyran - 4 - yloxy) - estr - 4 - en - 3 - one.

6. The compound selected from those of Claim 4 wherein R^1 is methyl and R^2 is hydrogen; 17β - (tetrahydropyran - 4 - yloxy) - androst - 4 - en - 3 - one.

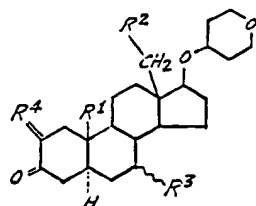
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7. The compound selected from those of Claim 4 wherein R^1 is hydrogen and R^2 is methyl; 17β - (tetrahydropyran - 4 - yloxy)-18 - methylestr - 4 - en - 3 - one.

5 8. The compound selected from those of Claim 4 wherein each of R^1 and R^2 is methyl; 17β - (tetrahydropyran - 4 - yloxy)-18 - methylandro - 4 - en - 3 - one.

9. A compound according to Claim 2 wherein R^1 is methyl, R^2 is hydrogen, and R^3 is methyl.

10. A compound selected from those of Claim 1 of the formula:



15 wherein each of R^1 , R^2 , R^3 , and R^4 is as therein defined.

11. A compound selected from those of Claim 10 wherein R^3 is hydrogen and R^4 is the group



in which R^5 is hydrogen.

12. The compound selected from those of Claim 11 wherein R^1 is methyl and R^2 is hydrogen; 17β - (tetrahydropyran - 4 - yloxy) - 5α - androstan - 3 - one.

13. The compound selected from those of Claim 11 wherein each of R^1 and R^2 is hydrogen; 17β - (tetrahydropyran - 4 - yloxy)- 5α - estran - 3 - one.

14. The compound selected from those of Claim 11 wherein R^1 is hydrogen and R^2 is methyl; 17β - (tetrahydropyran - 4 - yloxy) - 18 - methyl - 5α - estran - 3 - one.

15. The compound selected from those of Claim 11 wherein each of R^1 and R^2 is methyl; 17β - (tetrahydropyran - 4 - yloxy)-18 - methyl - 5α - androstan - 3 - one.

16. The compound according to Claim 10 wherein R^1 is methyl, R^2 is hydrogen, R^3 is hydrogen and R^4 is the group



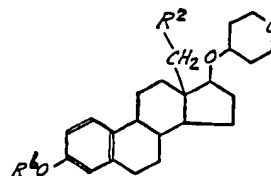
in which R^5 is methyl; 2α - methyl - 17β - (tetrahydropyran - 4 - yloxy) - 5α - androstan - 3 - one.

17. A compound according to Claim 10 wherein R^1 is methyl, R^2 is hydrogen, R^3 is methyl and R^4 is the group



in which R^5 is hydrogen.

18. A compound selected from those of Claim 1 of the formula:



wherein each of R^2 and R^6 is as therein defined.

19. A compound selected from those of Claim 18 wherein R^2 is methyl.

20. A compound selected from those of Claim 18 wherein R^2 is hydrogen.

21. The compound selected from those of Claim 20 wherein R^6 is hydrogen; 17β - (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - trien - 3 - ol.

22. The compound selected from those of Claim 20 wherein R^6 is acetyl; 3 - acetoxy- 17β - (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - triene.

23. The compound selected from those of Claim 20 wherein R^6 is benzoyl; 3 - benzoxyloxy - 17β - (tetrahydropyran - 4 - yloxy) - estra - 1,3,5(10) - triene.

24. The compound selected from those of Claim 20 wherein R^6 is methyl; 3 - methoxy - 17β - (tetrahydropyran - 4 - yloxy)-estra - 1,3,5(10) - triene.

25. A compound according to Claim 1, substantially as herein described and exemplified.

26. A pharmaceutical composition comprising a compound of Claim 1 in a suitable pharmaceutical excipient.

MEWBURN, ELLIS & CO.,
Chartered Patent Agents,
70/72 Chancery Lane,
London, WC2A 1AD.
Agents for the Applicants.

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